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ORIGINAL RESEARCH

Traumatic Brain Injury Outcomes After Recreational Cannabis Use

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Purpose: Basic science data indicate potential neuroprotective effects of cannabinoids in traumatic brain injury (TBI). We aimed to evaluate the effects of pre-TBI recreational cannabis use on TBI outcomes.

Patients and Methods: We used i2b2 (a scalable informatics framework; www.i2b2.org) to identify all patients presenting with acute TBI between 1/1/2014 and 12/31/2016, then conducted a double-abstraction medical chart review to compile basic demographic, urine drug screen (UDS), Glasgow Coma Scale (GCS), and available outcomes data (mortality, modified Rankin Scale (mRS), duration of stay, disposition (home, skilled nursing facility, inpatient rehabilitation, other)) at discharge and at specific time points thereafter. We conducted multivariable nested ordinal and logistic regression analyses to estimate associations between cannabis use, other UDS results, demographic factors, and selected outcomes.

Results: i2b2 identified 6396 patients who acutely presented to our emergency room with TBI. Of those, 3729 received UDS, with 22.2% of them testing positive for cannabis. Mortality was similar in patients who tested positive vs negative for cannabis (3.9% vs 4.8%; $p = 0.3$) despite more severe GCS on admission in the cannabis positive group ($p = 0.045$). Several discharge outcome measures favored the cannabis positive group who had a higher rate of discharge home vs other care settings ($p < 0.001$), lower discharge mRS ($p < 0.001$), and shorter duration of hospital stay ($p < 0.001$) than the UDS negative group. Multivariable analyses confirmed mostly independent associations between positive cannabis screen and these post-TBI short- and long-term outcomes.

Conclusion: This study adds evidence about the potentially neuroprotective effects of recreational cannabis for short- and long-term post-TBI outcomes. These results need to be confirmed via prospective data collections.

Keywords: cannabis, traumatic brain injury, Glasgow Coma Scale, GCS, outcomes, modified Rankin Scale, mRS

Introduction

Every year, traumatic brain injury (TBI) affects over 2 million individuals in the US with a global estimate of 69 million new cases.[1,2] Among various negative long-term sequelae, deficits in information processing, attention, working memory, and executive functioning occur in up to 65% of TBI survivors.[3] These deficits interfere with independence and reintegration into society, affect family functioning and well-being, and produce significant caregiver strain.[4,5] However, despite many past studies, there is no specific treatment to ameliorate the emergence of post-TBI deficits.[6,7] Thus, it is important to develop investigations into the factors that shape post-TBI outcomes.

In response to TBI, brain undergoes many primary and secondary structural, metabolic, and vascular changes.[8–10] These changes include increases in pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α[11–14] and changes in molecular pathways for chronic inflammatory transmitters such as vascular cell adhesion molecule-1 (VCAM-1) and cannabinoid receptor-2 (CB_2R), a marker of neuroinflammation predominantly expressed in activated microglia.[15–17] There is evidence that the neuroinflammatory cascade is involved in producing some of the deficits seen after TBI[18–23] and that blocking neuroinflammation during the acute phase of TBI may be neuroprotective.[24,25] As part of the neuro-metabolic response to TBI, the endocannabinoid system (ECS) offers a potential route for modifying neuroinflammation via its interactions with neurons and glia.[26,27] The interaction between

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phytocannabinoids, terpenes, and flavonoids and the ECS and other homeostatic systems has been studied in a substantial detail.[28] This includes not only anti-inflammatory and neuroprotective investigations but also research into the effects of phyto- and endocannabinoids on epileptogenesis and cognition.[29–31] Thus, basic and clinical science work has made important strides toward understanding the divergent roles of the ECS and the dynamics of its receptors (CB_1R/CB_2R) and neurotransmitters (2-arachidonoylglycerol (2-AG); anandamide (ANA)).[27,32] However, while elevated levels of endocannabinoids have been reported in response to TBI,[7,32] the roles of the ECS and of the phytocannabinoids in post-TBI recovery and their therapeutic potentials remain to be fully explored.

Recreational cannabis use in general population is common and growing. In the United States, recreational cannabis smoking increased from 7% in 2013 to 17% in 2023 (https://news.gallup.com/poll/284135/percentage-americans-smoke-marijuana.aspx). The global annual prevalence of recreational cannabis use has been estimated at 2.5% (www.who.int); approximately 45% of TBI victims report daily use of cannabis for the relief of their post-TBI symptoms.[33] On the clinical level, cannabis is known to exert multiple effects on working memory, coordination, and mood and its use has been linked to the increased incidence of motor vehicle accidents and associated with them TBIs, both of which are a result of "cannabis impaired driving".[34] Animal studies have shown that some of the cannabis plant constituents (eg, cannabidiol (CBD) or tetrahydrocannabinol (Δ^9-THC)) or cannabinoid analogues (eg, dexanabinol) have neuroprotective properties in animal models of ischemic or traumatic brain injury and could decrease mortality and improve outcomes after TBI.[35,36] Further, studies have also documented anti-seizure and anti-epileptogenic properties of some cannabinoids.[30,37] However, while a preliminary Phase II randomized controlled trial (RCT) showed a better Glasgow Outcomes Scale (GOS) at 3 months in patients receiving dexanabinol after TBI when compared to placebo,[38] an adequately powered RCT of dexanabinol was not successful in showing its superiority over placebo in extending life or improving outcomes after TBI.[35] The main criticism of this particular RCT is that dexanabinol is a synthetic rather than a naturally occurring cannabinoid and that the study was limited to a single synthetic cannabinoid molecule rather than a plant-derived assembly of various phytocannabinoids, terpenes, and flavonoids, many of them with specific therapeutic potential.[28]

A previous study reported that there is decreased mortality after TBI when victims tested positive for cannabis on serum toxicology screen.[39] In that study, positive urine cannabis toxicology screen (Tox(+)) was associated with lower mortality in univariate and multivariate analyses. In another TBI study, survival advantage in cannabis positive group was only observed in univariate analyses and it disappeared in multiple logistic regression.[40] The report from the National Academies of Science, Engineering, and Medicine in Conclusion 15 indicated that there is "limited evidence of a statistical association between cannabinoids and better outcomes after TBI or intracranial hemorrhage".[41] Despite a substantial body of literature postulating potential efficacy of cannabinoids in decreasing short- and long-term effects of TBI and improving post-TBI recovery, this research avenue is not well developed. This may be, in part, due to federal restrictions on cannabis use and research.[42] Thus, the first aim of the present study was to replicate the survival analyses conducted in the previous acute TBI study.[39] The second aim was to determine if, in addition to subjective measures, such as Glasgow Coma Scale (GCS) or modified Rankin Scale (mRS), more objective measures, such as duration of hospital stay and discharge disposition would be more favorable in patients who present with Tox(+) for cannabis compared with those who test negative (Tox(-)).

Materials and Methods

We conducted a retrospective chart review that spanned from the time of acute TBI to the last available clinical encounter (up to 9 years). Due to the retrospective nature of the data collection, the University of Alabama at Birmingham Institutional Review Board (UAB IRB) approved waiver of consent for the study. The study approval and the waiver of consent were issued because the IRB determined that "the research involves no greater than minimal risk and no procedures for which written consent is normally required outside the research context". The data collection and analyses were carried out in accordance with the Declaration of Helsinki ethics principles; data were deidentified before analyses were conducted. All individuals presenting to the UAB Emergency Room (ER) with a possible acute head trauma between 1/1/2014 and 12/31/2016 were identified via i2b2 tool (a scalable informatics framework) supported by the UAB Center for Clinical and Translational Science (CCTS; www.uab.edu/ccts/). i2b2 is supported by the National Institutes of Health (NIH)/the National Center for Biomedical Computing (https://www.i2b2.org/) and available to all registered and approved investigators. While our cohort may have some unique features (eg, racial distribution specific to our area), the

methodological approach to patient identification is reproducible because of the wide availability of the i2b2 tool. The 3-year time span was selected to allow sufficient numbers of participants to be identified, and, concurrently, to allow for at least 2 years of follow-up data to be available for review (in some patients, follow-up data were available for up to 9 years). i2b2 is specifically designed for cohort identification to allow searches for de-identified health information within electronic medical record (EMR) based on specific inclusion and exclusion criteria. i2b2 identified 6396 individuals who presented with the diagnosis of possible acute TBI during the study period. All chart entries between the incident TBI visit and the last chart review were reviewed, and charts of patients meeting inclusion criteria were fully abstracted. Inclusion criteria were ≥18 years of age at the time of presentation, definite acute TBI by description and/or imaging, and presenting within <24 hours of the acute TBI. Patients presenting >24 hours after TBI or with unclear history (eg, unconscious patients with multi-organ trauma but no evidence of cranial injury present on examination or imaging) were excluded. The 24 hour cut-off was selected as the earliest feasible timing of a neuroprotective or anti-epileptogenic intervention administration is up to 24 hours after injury.[43] Standardized case report form and data dictionary with explicit, pre-specified definitions of all collected measures were used.

Four clinical coordinators and the PI abstracted the records. Initially, each record was independently abstracted and double-entered (~25% of charts) by one of the trained clinical coordinators and the PI. Results were compared, and any differences were reconciled until consensus was reached. Once >95% agreement in the extracted data between the coordinator and the PI was reached, approximately 20% of the remaining data points abstracted by the coordinators were randomly reviewed by the PI for extraction accuracy, with any identified discrepancies discussed until consensus was reached. Each coordinator reviewed up to 1000 charts with the PI reviewing and partially or completely abstracting all records with particular attention to the entry criteria and outcome measures.

The main variables of interest were the standard qualitative urine drug screen (UDS) and the outcomes measured with modified Rankin Scale (mRS),[44] duration of hospital stay (in days), mortality, and discharge disposition. The UDS had to be performed at our institution or formal report had to be available upon transfer from the site of initial presentation. UDS data were extracted as performed (Yes/No) and, when performed, whether UDS was qualitatively positive/negative for cannabis (Tox(+)/Tox(-)), opioids, and other toxicology products (eg, stimulants); ethanol (EtOH) level was assessed in a separate test. Quantitative UDS was not obtained. Duration of hospital stay was coded as 1, 2, 3, and 4 or more days for descriptive and bivariate analyses, then recoded as 1–3 versus 4 or more days for multivariable modeling. Discharge outcomes included mortality (dead/alive), care disposition (home, skilled nursing home, inpatient rehabilitation, other), discharge mRS (a 7-category ordered measure: 0 = no disability, 1 = minimal disability, 2 = mild disability, 3 = moderate disability, 4 = moderate to severe disability, 5 = severe disability, and 6 = patient deceased).[45,46] The same measures were collected at 3, 6, 12, and 24 months after TBI and at the last available visit (up to 9 years after the initial TBI presentation in some patients). mRS was derived from EMR only if sufficient history and examination were available (eg, neurology, rehabilitation, or primary care provider evaluations); if not available, record/scoring of mRS was not included. Good agreement (>0.7) is noted between electronic medical records reviewers if they are trained medical professionals with even higher agreement seen when mRS is stratified between favorable and poor outcomes as above.[44] mRS was coded as a 7-category variable in descriptive and bivariate analyses, then recoded as favorable (0–2; no, minimal, or mild disability) versus poor (3–6; moderate, moderate-severe, severe, or deceased), per past literature[45,46] for multivariable modeling.

We also collected age, biological sex and, when available, self-reported race (coded as Black/African American vs White; other races and unknown race were computed for descriptive analyses then excluded from multivariable analyses), Hispanic ethnicity (only used for sample description), current/past substance use history, history of mental health disorders (Yes/No), results of CT (normal, hemorrhage eg, subdural, subarachnoid, and/or parenchymal, more than one type of injury, extra-cranial injury, or other type of injury, eg, penetrating skull fracture or diffuse axonal injury). Admission TBI severity was measured with earliest available (reported) GCS stratified as mild (GCS 14–15), moderate (GCS 9–13), and severe (GCS 3–8).[47,48] Since GCS is a standard measure performed typically at the first contact (emergency room physician at arrival), the scores were available in the record. Dummy variables were constructed for the three GCS categories: mild, moderate, and severe, for use as an independent variable in multivariable analyses.

Statistical analyses were conducted using IBM SPSS Version 28.0 (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). First, frequency distributions of demographic and clinical outcome variables were computed for the

full sample and by cannabis screening status (Tox(+)/Tox(-)). Differences between groups were analyzed using Chi-square tests. In addition, *t*-test was used to compare mean age between Tox(+) and Tox(-) groups. Next, regression analyses were conducted to evaluate the association between cannabis screen result and selected outcomes: GCS (ordinal regression (PLUM procedure)) and duration of hospital stay and discharge mRS (logistic regressions), alone and adjusting for other toxicology screens (EtOH, opioids, and multiple/other substances) and sociodemographic variables (age at admission, biological sex, and Black/African American vs White race). The selected outcomes were modeled in a nested fashion starting with a model including only the cannabis screen variable, then adding other drug screens, and finally adding sociodemographic variables. Both unadjusted and adjusted models are presented if there are clear differences between the models; otherwise, only final/fully adjusted models are shown. Associations were considered significant at the 0.05 alpha level.

Results

Of the 6396 potential study candidates identified by i2b2, 3729 had definite head trauma within <24 hours of presentation and received UDS, and they constitute the study cohort. 2667 were excluded because they were younger than 18 years of age, did not have definite TBI, presented >24 hours after acute TBI, or did not have UDS. A total of 22.2% of the cohort had a positive cannabis screen (Tox(+)). Table 1 outlines the clinical characteristics of this sample. Compared to patients with a negative cannabis screen, patients with a positive cannabis screen were significantly younger ($p < 0.001$) at the time of TBI (mean = 32.5 years [SD = 12.3] vs 44.5 years [SD = 18.3]), more likely to be male ($p < 0.001$), and more likely to admit to current substance use ($p < 0.001$). The sample was 29.6% Black/African American and 68.0% White which is reflective of the Alabama population; 1.2% were "other" and 0.8% were "unknown" race. The proportion of Black/African American individual with Tox(+) in the sample was higher than White individuals (46.9% vs 52.2%; $p < 0.001$). 3.5% of the sample was Hispanic/Latinx.

Table 2 shows the distribution of emergency room and discharge outcomes by cannabis screen status. Overall, Tox(+) patients had a higher proportion of initial GCS scores in the severe range and a lower proportion in the mild range ($p = 0.045$),

Table 1 Characteristics of Patients Who Received ER Toxicology Screen for Cannabis – by Screen Result: positive=Tox(+) versus negative=Tox(-)

	All	Tox (+)	Tox (-)	p
	%	%	%	
Total sample (n = 3729)	*100.0*	*22.2*	*77.8*	
Age at admission				< 0.001
29 years and younger	32.8	50.5	27.8	
30–39 years	18.6	23.5	17.2	
40–49 years	16.5	14.2	17.2	
50–59 years	14.5	8.6	16.2	
60–69 years	9.5	3.0	11.4	
70 years and older	8.1	0.2	10.3	
Biological sex				< 0.001
Male	68.0	75.3	65.9	
Female	32.0	24.7	34.1	
Race				< 0.001
White	68.4	52.2	73.0	
Black/African American	29.6	46.9	24.6	
Other	1.2	0.4	1.4	
Unknown	0.8	0.6	0.9	
Ethnicity				< 0.001
Hispanic/Latinx	3.5	0.7	4.3	
Not Hispanic/Latinx	95.5	98.5	94.6	
Unknown	1.0	0.7	1.1	

(*Continued*)

Table 1 (Continued).

	All	Tox (+)	Tox (-)	p
	%	%	%	
Current substance user				< 0.001
Yes, within last 3 months	15.9	32.3	11.2	
Not within last 3 months	1.0	0.6	1.2	
Never	60.5	42.3	65.7	
Unknown	22.6	24.8	21.9	
Recent drug use - drug type				< 0.001
Cannabis	5.2	16.7	2.0	
Other drug/s	10.9	14.8	9.8	
Unknown or non-user	83.9	68.5	88.2	
Mental disorder before TBI				
Yes	13.0	13.4	12.8	
No	72.0	69.1	72.8	
Unknown	15.0	17.4	14.4	
CT in ER[a]				0.139
Done	99.4	99.0	99.5	
Not done	0.6	1.0	0.5	

Note: [a]n = 3711; 18 (0.5%) missing.
Abbreviations: ER, emergency room; TBI, traumatic brain injury; CT, computed tomography.

Table 2 ER and Discharge Outcomes of Patients[a] Who Received ER Toxicology Screen for Cannabis – by Screen Result: Positive = Tox(+) versus Negative = Tox(-)

	All	Tox (+)	Tox (-)	p
	%	%	%	
GCS[b]				0.045
Severe (3–8)	14.6	17.3	13.8	
Moderate (9–13)	8.5	8.2	8.5	
Mild (14–15)	76.9	74.5	77.6	
CT in ER results[c]				0.017
Normal	24.8	25.7	24.6	
Subarachnoid, subdural, and/or parenchymal hemorrhage	15.1	11.3	16.2	
More than one type of injury	14.5	15.7	14.2	
Extra cranial injury	44.1	45.7	43.6	
Other (diffuse axonal injury, penetrating injury, or skull fracture)	1.5	1.6	1.5	
ASM prescribed at admission[d]				0.816
Yes	12.1	11.9	12.2	
No	87.9	88.1	87.8	
ASM prescribed at discharge[d]				0.318
Yes	19.5	18.3	19.8	
No	80.5	81.7	80.2	
ASM regimen at admission[d]				0.197
Phenytoin	0.3	0.6	0.2	
Levetiracetam	6.2	6.8	6.1	
Other	11.7	10.3	12.1	
More than one	1.9	1.7	2.0	
No seizure meds	79.9	80.6	79.7	

(*Continued*)

Table 2 (Continued).

	All	Tox (+)	Tox (-)	p
	%	%	%	
Outcome at hospital discharge[d]				0.300
Alive	95.4	96.1	95.2	
Deceased	4.6	3.9	4.8	
Disposition at hospital discharge[d]				<0.001
Home	76.6	83.9	74.5	
Skilled nursing home	5.3	2.3	6.1	
Inpatient rehabilitation	10.6	6.9	11.7	
Other	7.5	6.9	7.7	
Discharge mRS[d]				<0.001
No disability	32.1	49.2	27.2	
Minimal - able to carry all activities	26.2	22.8	27.2	
Mild - able to carry most activities	13.7	9.0	15.0	
Moderate - still able to walk and carry some activities	13.8	8.7	15.2	
Moderate-severe - unable to walk and needs assistance with body functions	7.4	5.0	8.1	
Severe - bedridden with constant assistance	2.2	1.6	2.4	
Deceased	4.6	3.9	4.8	
Duration of stay (days)[e]				<0.001
1	41.9	49.5	39.8	
2	8.1	7.2	8.4	
3	6.9	6.8	6.9	
4 or longer	43.1	36.6	45.0	
Duration of stay (days), if not deceased[e]				<0.001
1	41.9	49.5	39.8	
2	8.1	7.2	8.4	
3	6.9	6.8	6.9	
4 or longer	43.1	36.6	45.0	

Notes: [a]n = 3729. [b]n = 3723; 6 (0.2%) missing. [c]n = 3711; 18 (0.5%) missing. [d]n = 3728; 1 missing. [e]Duration of hospital stay is provided for all and separately for only those who survived the first 24 hours since the numbers of deceased participants were higher (non-significant) in the Tox (-) group.
Abbreviations: ER, emergency room; GCS, Glasgow Coma Scale; CT, computed tomography; ASM, anti-seizure medications; mRS, modified Rankin Scale.

indicating that the Tox(+) group had overall more severe TBI at the time of presentation. Among the 99.5% of patients who received CT, the proportions of normal CT scan results and of only extra-cranial injury were higher in the Tox(+) group than the Tox(-) group ($p = 0.017$). There were no differences between the groups in the proportion of patients who received anti-seizure medications (ASMs; 11.9% vs 12.1%; $p = 0.318$) or which ASMs were used (phenytoin vs levetiracetam vs other ASMs; $p = 0.197$).

Among discharge outcomes, the overall percentage of deceased patients in the Tox(-) group was higher than in the Tox(+) group (4.8% vs 3.9%), but this difference was not significant ($p = 0.3$). Tox(+) patients were more likely to be discharged home (83.9% vs 74.5%; $p < 0.001$) rather than to skilled nursing homes, rehabilitation facilities, or other facilities. Also, the Tox(+) group had overall lower disability as measured with mRS when compared to those who were Tox(-) – 49.2% of those who were Tox(+) had mRS = 0 (no disability) compared to 27.2% of those who were Tox(-) on admission ($p < 0.001$). Finally, the duration of hospital stay for Tox(+) patients was typically shorter than of those who were Tox(-). A smaller proportion (36.7%) of patients with Tox(+) had a stay of 4 days or longer compared to patients with Tox(-) (45.5%, $p < 0.001$; Table 2).

In Table 3, we present mRS data stratified by favorable vs poor discharge outcome.[45] At all time points, the proportion of patients with a favorable outcome was higher in those presenting with Tox(+) than in those presenting with Tox(-). These differences were significant (ps ≤ 0.015) at discharge, 3 and 6 months, and at the last available follow-up.

Before proceeding to regression analyses, we examined distributions of the study outcomes (mortality, mRS, duration of stay, disposition) at discharge and at specific time points thereafter across groups with positive and negative screens

Table 3 Intermediate and Long-Term mRS Score of Patients Who Received ER Toxicology Screen for Cannabis – by Screen Result: positive=Tox(+) versus negative=Tox(-)

	All	Tox (+)	Tox (-)	p
	%	%	%	
Discharge mRS (n = 3728)				<0.001
Favorable	72	80.9	69.4	
Poor	28	19.1	30.6	
3-month mRS (n = 1585)				0.011
Favorable	71.1	76.7	69.6	
Poor	28.9	23.3	30.4	
6-month mRS (n = 855)				0.014
Favorable	87	92.6	85.6	
Poor	13	7.4	14.4	
12-month mRS (n = 560)				0.073
Favorable	88.8	93.3	87.5	
Poor	11.3	6.7	12.5	
24-month mRS (n = 346)				0.631
Favorable	90.5	91.9	90.1	
Poor	9.5	8.1	9.9	
Last mRS (n = 1361)				0.015
Favorable	91.7	94.9	90.7	
Poor	8.3	5.1	9.3	

Abbreviations: ER, emergency room; mRS, modified Rankin Scale (0–2 considered favorable, 3–6 considered poor).

for EtOH, opioids, and multiple/other substances (Table S1). All screen types had associations with GCS (ps < 0.001), but few differences were observed in discharge and follow-up mRS based on other UDS results. Only patients with positive screens for multiple/other substances had worse discharge mRS compared to their negative screen counterparts. Also, more patients with a positive screen for opioids had favorable 3- and 6-month mRS compared to patients with a negative opioid screen.

The regression results predicting selected outcomes (GCS, duration of hospital stay, and discharge mRS) are shown in Tables 4–6. Ordinal regression modeling GCS (Table 4A) shows positive cannabis screen to be associated with more severe GSC scores in the unadjusted model (coefficient = 0.198, p = 0.032). After adjusting for other toxicology screens in the next model (Table 4B), cannabis screen is no longer significant (p = 0.327) while the other toxicology screens are all predictive of GSC levels (ps ≤ 0.012) in the way which is consistent with bivariate analysis results: screens positive for EtOH and multiple/other substances are associated with higher (milder) GSC whereas the association is reverse for opioid screen. These results suggest that presence of substances other than cannabis may be responsible for differences in GCS and mRS levels to a greater extent than the presence of cannabis alone.

The logistic regression results (final/full model) predicting duration of hospital stay (Table 5) indicate positive cannabis screen to be associated with shorter (1–3 day) hospital stay (b = 0.367, p < 0.001) independently of all other variables, including ER CT status, GCS category, positive screens for other substances, and socio-demographics (age, sex, and Black/African American race). Among the other variables, as expected, normal CT and less severe GCS were associated with shorter stay while older age was associated with longer stay (ps < 0.001). In addition, screens positive for opioids and other/multiple substances were associated with longer stay (ps < 0.001), but EtOH screen had no association (p = 0.147). There were also no sex (p = 0.632) and Black/African American-White race (p = 0.685) differences in duration of hospital stay.

Lastly, the logistic regression results (final/full model) predicting discharge mRS (Table 6) indicate positive cannabis screen to be associated with favorable (0–2) mRS (b = 0.733, p < 0.001) independently of all other variables including

Table 4 Ordinal Regression (PLUM) Predicting GCS Categories (Severe, Moderate, Mild) by Cannabis Screen (Unadjusted Model) and Adjusting for Other Substance Screens in Patients Who Received ER Toxicology Screen for Cannabis (n = 3622)

A. Unadjusted model		**Estimate**	**Std. Error**	**Wald**	***df***	**Sig.**	**95% Confidence Interval**	
							Lower Bound	**Upper Bound**
Threshold	[GCS=0]	−1.629	0.084	375.137	1	<0.001	−1.794	−1.464
	[GCS=1]	−1.059	0.08	173.926	1	<0.001	−1.216	−0.901
Location	[Cannabis screen=0]	0.198	0.092	4.625	1	0.032	0.018	0.378
	[Cannabis screen=1]	0			0			
Link function: Logit.								
Model Fitting Information								
	−2 Log Likelihood	Chi-Square	*df*	Sig.				
Intercept Only	35.235							
Final	30.738	4.498	1	0.034				
B. Adjusted model[a]		**Estimate**	**Std. Error**	**Wald**	***df***	**Sig.**	**95% Confidence Interval**	
							Lower Bound	**Upper Bound**
Threshold	[GCS=0]	−1.655	0.123	179.588	1	<0.001	−1.897	−1.413
	[GCS=1]	−1.041	0.121	74.133	1	<0.001	−1.278	−0.804
Location	[Cannabis screen=0]	0.094	0.096	0.96	1	0.327	−0.094	0.282
	[Cannabis screen=1]	0			0			
	[EtOH screen=0]	0.218	0.087	6.318	1	0.012	0.048	0.388
	[EtOH screen=1]	0			0			
	[Opioids screen=0]	−1.076	0.091	140.689	1	<0.001	−1.253	−0.898
	[Opioids screen=1]	0			0			
	[Other/multiple drug screen=0]	1.109	0.084	174.914	1	<0.001	0.944	1.273
	[Other/multiple drug screen=1]	0			0			
Link function: Logit.								
Model Fitting Information								
	−2 Log Likelihood	Chi-Square	*df*	Sig.				
Intercept Only	477.879							
Final	179.447	298.432	4	<0.001				

Notes: [a]Model could not be adjusted for age/age categories, sex, and Black race due to too many cells with zero frequencies. In other analyses (not shown), age had a negative association with GCS (higher age associated with less favorable GCS scores) while sex and Black/African American (vs White) race showed no association with GCS. GCS is coded as severe=0, moderate=1, mild=2. Drug screens are dummy-coded, with positive screen coded as 1.
Abbreviations: ER, emergency room; GCS, Glasgow Coma Scale; EtOH, ethanol.

emergency room CT status, GCS category, positive screens for other substances, and socio-demographics (age, sex, and Black/African American race). As expected, normal CT and less severe GCS were associated (ps < 0.001) with favorable mRS while older age was associated with poor mRS. In addition, positive EtOH screen was associated with favorable mRS (p = 0.011) while positive opioid screen was associated with poor mRS (p < 0.001) at discharge; screen for multiple/other substances had no association (p = 0.680). There were no sex and racial differences in discharge mRS (ps ≥ 0.447).

Discussion

The first aim of this study was to assess the survival of patients presenting with TBI as it relates to recent recreational cannabis use. While the mortality in our study was, as expected, higher in the Tox(-) for cannabis group, this difference was not significant and, thus, we were unable to replicate the significant survival advantage of cannabis reported in the previous study.[39] However, the lack of cannabis advantage for survival after TBI observed in our study is partially in agreement with another study where cannabis conferred advantage only in univariate but not multivariate analyses.[40] Our second goal was to evaluate the relationship between cannabis screen status and TBI severity (GCS) at presentation

Table 5 Logistic Regression Predicting Duration of Hospital Stay (1–3 Days versus 4 Days or Longer) in Patients Who Received ER Toxicology Screen for Cannabis (n = 3622)

	B	Std. Error	Wald	*df*	Sig.	Exp(B)
Cannabis screen positive	0.367	0.093	15.567	1	<0.001	1.444
ER CT normal	0.725	0.088	67.327	1	<0.001	2.064
GCS Moderate	0.554	0.155	12.787	1	<0.001	1.74
GCS Mild	1.385	0.111	154.592	1	<0.001	3.994
EtOH screen positive	0.117	0.081	2.101	1	0.147	1.124
Opioids screen positive	−0.513	0.076	46.128	1	<0.001	0.599
Other/multiple drug screen positive	−0.31	0.076	16.532	1	<0.001	0.734
Age at admission	−0.011	0.002	29.39	1	<0.001	0.989
Female (vs male)	0.037	0.077	0.229	1	0.632	1.038
Black/African American (vs White)	−0.033	0.081	0.165	1	0.685	0.968
Constant	*−0.298*	*0.149*	*3.972*	*1*	*0.046*	*0.742*
−2 Log likelihood	*4519.007*					
Cox & Snell R Square	*0.113*					
Nagelkerke R Square	*0.152*					

Notes: GCS Severe is the reference category (omitted). Other/unknown race was excluded from the analysis.
Abbreviations: ER, emergency room; GCS, Glasgow Coma Scale; EtOH, ethanol.

Table 6 Logistic Regression Predicting Discharge mRS (Favorable = 1–2 versus Poor = 3–6) in Patients Who Received ER Toxicology Screen for Cannabis (n = 3622)

	B	Std. Error	Wald	*df*	Sig.	Exp(B)
Cannabis screen positive	0.733	0.119	38.061	1	<0.001	2.082
ER CT normal	0.373	0.105	12.553	1	<0.001	1.452
GCS Moderate	1.803	0.163	122.802	1	<0.001	6.07
GCS Mild	2.607	0.123	448.868	1	<0.001	13.565
EtOH screen positive	0.244	0.096	6.424	1	0.011	1.276
Opioids screen positive	−0.352	0.088	15.910	1	<0.001	0.703
Other/multiple drug screen positive	−0.037	0.089	0.170	1	0.680	0.964
Age at admission	−0.015	0.002	37.705	1	<0.001	0.985
Female (vs male)	0.068	0.09	0.579	1	0.447	1.071
Black/African American (vs White)	0.001	0.095	0.000	1	0.993	1.001
Constant	*−0.646*	*0.167*	*14.889*	*1*	*<0.001*	*0.524*
−2 Log likelihood	*3596.778*					
Cox & Snell R Square	*0.177*					
Nagelkerke R Square	*0.255*					

Notes: GCS_severe is the reference category (omitted). Other/unknown race was excluded from the analysis.
Abbreviations: mRS, modified Rankin Scale; ER, emergency room; CT, computed tomography; GCS, Glasgow Coma Scale; EtOH, ethanol.

and to evaluate various subjective and objective measures of post-TBI outcomes such as mRS at discharge, duration of hospital stay, and discharge disposition and mRS throughout multiple time points after TBI including last available follow-up. These analyses indicated better short- and long-term outcomes in patients who presented with TBI and Tox(+) for cannabis, compared to Tox(-) patients.

The first finding of our study is the lack of a relationship between mortality and cannabis UDS status, which is in direct contrast to the study by Nguyen et al.[39] However, some differences in approaches between these two studies and cohorts may be responsible for the divergent findings. First, the cohort identification methodology differed between these two studies. In the Nguyen et al study, participants were identified based on the trauma team activations – it is not clear

from the study description whether minor traumas (eg, concussions not associated with any other injuries) were included or excluded. In contrast, our i2b2 screen included all patients who presented with (and who received evaluation for) any type of head trauma including patients with normal CT or CT with evidence of only extra-cranial injury (24.8% and 44.1%, respectively). Furthermore, the initial severity of TBI was measured differently in the two studies – the head Abbreviated Injury Score (AIS) in Nguyen et al vs the GCS in ours. While the GCS and the AIS may be similar in predicting long-term outcomes measured with the Glasgow Outcome Scale (GOS), their overall correlation with 12-month outcomes is weak.[49] Hence, we cannot directly compare severities of TBIs between the two studies. Further, the differences in approaches may be the reason for identifying in the same period (3 years) a much higher number of TBIs in our study (6396 vs 538 in the Nguyen et al study). Inclusion of participants with milder injuries may explain the proportionally lower overall mortality rate in our study (4.6 vs 9.9). However, even though not statistically significant, mortality was numerically higher among patients who tested negative for cannabis compared to their positive counterparts, underscoring the possibility that cannabis may need to be further investigated in the setting of moderate or severe TBI, as suggested by recent reviews.[7,28] Similarly difficult is the comparison to the study by Leskovan et al since their secondary outcome measures were days in intensive care unit, days on ventilator, and duration of stay.[40] The only comparable outcome measures were mortality at discharge and the duration of hospital stay. These authors showed that the mortality was significantly lower in the group positive for cannabis when compared to the no-drugs group. Further, the no-drugs group had significantly longer stay compared to the cannabis group which is in agreement with our data.[40]

Our other findings support the need for future studies of cannabis in TBI, including potential for testing and developing cannabis-based treatment approaches in this setting. Among patients who tested positive for cannabis, favorable disposition at hospital discharge was observed more often than in the Tox(+) group (home discharge 83.9% vs 74.5%; $p < 0.001$, respectively), despite the GCS being more severe at admission (severe range 17.3% vs 13.8%; $p = 0.045$, respectively). Further, 72% of Tox(+) patients had no or minimal disability on discharge compared to 54.4% of Tox(-) patients ($p < 0.001$) and the duration of hospital stay was shorter in the Tox(+) group ($p < 0.001$). These results suggest possible positive effects of cannabis on the initial outcomes of TBI and indicate that the presence of cannabis may have neuroprotective effects.[50] However, this interpretation warrants caution, as there may be other factors such as frequency and dose of cannabis use or the exact timing since the last use that were not available in the current retrospective study. Prospective approaches are needed to investigate these and other factors. In addition, the composition and the content and proportions of cannabinoids, even the major ones eg, CBD vs Δ^9-THC, in recreational cannabis products such as those used by our patients, are typically unknown and may vary considerably.[51]

The positive effects of cannabis seen at discharge are further supported by continuously better outcomes measured with mRS at 3 and 6 months and at the last available visit (Table 3). While these are important long-term outcomes, they also need to be interpreted with caution, as the reliability and repeatability of mRS have been questioned.[52,53] However, 0.7 and higher agreement in mRS scoring between medically trained EMR reviewers as in our study has been recently noted.[44] Further, these and the previously discussed univariate analyses are mostly consistent with multivariate regression results (Tables 4–6) strengthening our results. Our findings are overall in line with the previously observed neuroprotective effects of various cannabinoids and are not necessarily in conflict with negative results of the dexanabinol trial that tested one synthetic cannabinoid rather than the plant-derived product with multiple constituents.[28,35,50] The entourage effect of all of the cannabinoids, terpenes, and flavonoids may be contributing to and enhancing the individual effects of specific cannabinoids such as CBD.[54] However, our study was not designed to evaluate this effect and it would not be possible to design such a study in an uncontrolled setting, where the intra- and inter-subject variability of the used cannabis products are likely high.

The limitations of our study include retrospective and non-randomized approach and the known weaknesses of the used scales/measures in assessing post-TBI outcomes. However, how to best measure severity of TBI[55] and outcomes in the post-TBI setting[45,55] is still being debated. Our results were obtained with standardized and widely used measures and provide a foundation for future studies of the effects of cannabinoids on post-TBI outcomes. We also acknowledge that we did not stratify TBI by specific etiology (eg, blunt vs penetrating trauma; presence vs absence of hemorrhage), and we lacked information about specific cannabinoid content and strength in the recreational products used by the patients. In addition, the recreational cannabis use has substantially increased in the US population (from 7% to 17%; https://news.

gallup.com/poll/284135/percentage-americans-smoke-marijuana.aspx) since around this data collection, so the study results may not be fully reflective of clinical outcomes in contemporary patient populations. Finally, the racial and ethnic background of our cohort was only partially reflective of the US population. As such, we cannot comment whether our results apply to all racial and ethnic groups in other US locations outside of Alabama. All of these factors could have affected the findings and should be considered in future research.

Conclusion

Available basic science and limited clinical data indicate potential neuroprotective effects of cannabinoids in traumatic brain injury (TBI). In this large retrospective study, we show that recreational cannabis use prior to TBI may confer neuroprotective short- and long-term benefits. These results need to be confirmed via prospective data collections.

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Disclosure

JPS reports grants from State of Alabama, serves or has served as a consultant/advisor for PureTech Health, Biopharmaceutical Research Company, AdCel Pharma, Serina Therapeutics Inc., and Greenwich Biosciences Inc. all of which develop cannabis-based medicines. MS has served as a consultant/advisor to Greenwich Biosciences Inc. which develops cannabis-based medicines. The authors report no other conflicts of interest in this work.

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